

REMARKS

Applicants submit herewith the following: (1) a copy of the Notice to Comply with Sequence Rules; (2) a substitute computer readable form (CRF) copy of the sequence listing as requested in the Notice and (3) a substitute paper copy of the sequence listing as requested in the Notice.

Statement Under 37 C.F.R. 1.821(f), 1.821(g) and 1.825(d)

The sequence listing information recorded in the substitute CRF is identical to the enclosed substitute written sequence listing. The data in the substitute CRF is identical to the data in the CRF originally filed April 14, 2003. No new matter is introduced by entering this sequence listing into the application. Thus, Applicants request entry of the sequence listing (substitute paper copy and substitute CRF) into the specification.

No fee is believed to be necessary in connection with the filing of this communication. However, if any fee is required, the Commissioner is hereby authorized to charge such fee(s) to Deposit Account No. 50-0540.

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Respectfully Submitted,



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Version with markings to show changes made

The paragraph that begins on page 8, line 15, and ends on page 9, line 11, has been replaced with the following paragraph:

According to an aspect of the present invention, compounds are provided that are useful for generating metal labeled imaging agents that are substantially free of the unlabeled imaging agent. The compounds include a metal support surface, and a conjugate releasably bound to the support surface. the conjugate is capable of coordinating with a complex-forming metal ion so that the conjugate is released (transchelated) from the support surface. The conjugate preferably includes a ligand and a targeting molecule. The conjugate is preferably a peptide, a polypeptide, a peptide for polypeptide mimetic (preferably a derivative) or an organic molecule. Those skilled in the art recognize that a variety of techniques are available for constructing peptide mimetics with the same or similar desired biological activity as a corresponding peptide or polypeptide compound of the invention but with more favorable activity with respect to solubility, stability, and/or susceptibility to hydrolysis and proteolysis. See for example, Morgan and Gainor, *Ann. Rep. Med. Chem.*, **24**:243-252 (1989). The organic molecule is preferably a small organic molecule, having molecular weight less than about 600 Daltons and more preferably less than about 500 Daltons. The ligand may be a peptide, a peptide mimetic or a small organic molecule. The ligand preferably incorporates (a) a surface binding group selected from the group consisting of a cysteine amino acid residue, a cysteine amino acid residue derivative, a thiol or thioether group attached to an organic molecule, an amino acid residue derivative including phosphorus and a phosphorus containing organic molecule, wherein the amino acid residue, amino acid residue derivative or organic molecule is capable of releasably binding to the support surface; and (b) at least one accessory group capable of coordinating with the complex-forming metal ion. In a variation of the invention it is possible that one or more accessory groups is in the targeting molecule. The conjugate is capable of coordinating with a complex-forming metal ion so that the conjugate is released from the support surface. The conjugate

preferably includes a peptide sequence such as a bombesin 7-14 fragment, QWAVGHLM (SEQ ID NO:1), TKPPR (SEQ ID NO:2), RGDS (SEQ ID NO:3), cyclopropylcarbonyl-nLe-L-F-W-E-K(GCSDMG)-G, an antibody (preferably monoclonal or polyclonal) antibody fragment and a small organic molecule that targets a receptor or a transporter.

Please replace the paragraph that begins on page 10, line 28, and ends on page 11, line 18, with the following paragraph:

Targeting molecule suitable for use in compounds of the invention are compounds that are capable of localizing selectively *in vivo* at sites for imaging such as at a particular organ, tissue or cell type. Suitable targeting molecules include a polypeptide, a peptide, a nucleic acid molecule, an oligonucleotide, a saccharide, an oligosaccharide, a steroid, a cyclic peptide, a peptide or polypeptide mimetic, an enzyme substrate, an inhibitor and a small organ molecule. Preferred targeting molecules include polypeptides and peptides, particularly those capable of binding with specificity to cell surface receptors characteristic of a particular pathology. The targeting molecule is preferably a molecule having agonist or antagonist activity. The targeting molecule preferably includes a molecule selected from the group consisting of a bombesin 7-14 fragment, QWAVGHLM (SEQ ID NO:1), TKPPR (SEQ ID NO:2), RGDS (SEQ ID NO:3) and small organic molecule that targets a receptor or a transporter. The receptor or transporter is preferably a dopamine receptor or transporter, a serotonin receptor or transporter, a sigma receptor, a GABA receptor, a nicotinic receptor, a cholinergic receptor, a norepinephrine receptor or transporter, a glucose transporter and an opioid receptor. Other preferable targeting molecules are peptides, polypeptides or derivatives comprising 3 or more amino acid residues that bind to cell surface receptors such as those described PCT/CA94/00395. Preferably, targeting molecules are peptides comprising about: 3 to 1000, 3 to 500, 3 to 100, 3 to 50 amino acids and more preferable 3 to 10 or 3 to 6 amino acids. Small organic molecules of preferably about: 6 to 500, 6 to 250, 6 to 100 carbons and more preferably about 6 to 50 or 6 to 25 carbons are also useful targeting molecules. In an embodiment, targeting molecules are chemotactic peptides that bind to cell surface receptors and in particular are chemotactic peptides that

incorporate the amino acid sequence cyclopropylcarbonyl-nLe-L-F-W-E-K(GCSDMG)-G.

Please replace the paragraph that occurs on page 20, lines 2-6, with the following paragraph:

RP414 (dimethylglycine-serine-cysteine (Acm)-glycine) (SEQ ID NO:4) 50mg was dissolved in 30% acetic acid and mercury acetate (75mg) added. The mixture was stirred at room temperature for [3.5h hydrogen] 3.5 hours. Hydrogen sulfide gas was bubbled through the solution with the formation of a black precipitate. This precipitate was removed by filtration and the solvents removed from the filtrate under reduced pressure.

Please replace the paragraph that begins on page 20, line 21, and ends on page 21, line 2, with the following paragraph:

RP527 (dimethylglycine-ser-cys(Acm)-gly-βala-gin-trp-ala-val-gly-his-leu-met-NH₂) (SEQ ID NO:5) (~10mg, 1eq) was dissolved in 30% acetic acid (4mL) and then mercuric acetate (2.2mg) was added. The reaction was left at room temperature for 3 hours and then bubbled through with hydrogen sulfide for 2 minutes. The resulting mixture was centrifuged and the solution decanted from the pellet of mercury sulfide. The solvent was removed in vacuo. RP527-SH(~10 mg) was then dissolved in a 1:1 solution of ethanol:0.01 PBS and added to the gold powder in a vacutainer with vigorous stirring (magnetic stirbar was added). The solution was flushed with argon for 10 minutes and left under argon at room temperature for 24 hours. The reaction mixture was centrifuged and the supernatant removed. The powder was washed with a 1:1 mixture of ethanol:aqueous 0.1% trifluoroacetic acid (5 X 4 mL), centrifuging between each addition of washing solution. The final aliquot was decanted off and the gold was dried in vacuo. It was purged with argon and stored at -20°C in preparation for labeling with Tc-99m.

Please replace the paragraph that occurs on page 21, lines 28-29, with the following paragraph:

This experiment was repeated with RP128 (dmG-S-C(Acm)-G-T-K-P-P-R) (SEQ ID NO:6) attached to gold foil (RP905).

Claims 13 and 14 have been amended as follows:

13. (Amended) The compound of any claims 1 to 12, wherein the targeting molecule comprises a molecule selected from the group consisting of a bombesin 7-14 fragment, QWAVGHLM (SEQ ID NO:1), TKPPR (SEQ ID NO:2), RGDS (SEQ ID NO:3) and a small organic molecule that targets a receptor or a transporter.

14. (Amended) The compound of any of claims 1 to 13, wherein the conjugate comprises a peptide sequence selected from the group consisting of a bombesin 7-14 fragment, QWAVGHLM (SEQ ID NO:1), TKPPR (SEQ ID NO:2), RGDS (SEQ ID NO:3) and small organic molecule that targets a receptor or a transporter.